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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WINSTON & STRAWN LLP
1700 K STREET, N.W.
WASHINGTON, DC 20006

EXAMINER	
HUMPHREY, DAVID HAROLD	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,661	YAYON ET AL.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-47 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-47 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Election/Restrictions

1. Claims 1, 2, and 3, link inventions I-XXX. Claim 44 links inventions LV-LXXXIV. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim 1, 2, 3, and 44. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I-XXX. Claims 4-10, 15-22, and 31, drawn to a molecule comprising the antigen-binding portion of an isolated antibody, respectively, which has an increased affinity for a receptor protein tyrosine kinase, respectively (see section 4, pages 5-9) and which blocks constitutive activation of the receptor tyrosine kinase, classified in class 530, subclass 387.1.

XXXI-LII. Claims 11-14, and 23-30, drawn to an isolated nucleic acid molecule, respectively (see section 5, pages 9-11), classified in class 536, subclass 23.1.

LIII. Claims 32-37, drawn to a method for treating or inhibiting a skeletal dyplasia or a craniosynostosis disorder, classified in class 424, subclass 133.1.

LIV. Claims 38-43, drawn to a method for treating or inhibiting a cell proliferative disease or disorder associated with abnormal RPTK activity, classified in class 424, subclass 809.

LV-LXXXIV. Claims 45-47, drawn to a method for screening a molecule by providing a library of antigen binding fragments and identifying an antigen binding fragment which binds to the dimeric form of the receptor protein tyrosine kinase, respectively (see section 6, pages 11-13), classified in class 435, subclass 7.1.

3. The inventions are distinct, each from the other because of the following reasons:

Inventions I-XXX and XXXI-LII are drawn to separate and distinct products. Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P § 806.05 for inventive groups that are directed to different products, restriction is deemed proper because these products constitute patentably distinct inventions. Groups I-XXX are drawn to antigen-binding portions of an antibody whereas Groups XXXI-LII are drawn to isolated nucleic acids. The antigen-binding portion of an antibody

is a protein. Proteins and nucleic acids have substantially different physical, chemical, structural and functional properties. Moreover, they are made using different techniques and reagents and have materially different modes of operation in vivo. DNA, deoxyribonucleic acids are unbranched polymers composed of four subunits while the antigen-binding portions of an antibody consist of polypeptides which are a linear order of amino acid residues.

Inventions LIII, LIV, and LV-LXXXIV, are separate and distinct methods. Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: they have separate and distinct method objectives, utilize different method steps, method parameters, and employ distinct reagents. For example, Invention LIII is drawn to a method of inhibiting a skeletal dysplasia or craniosyntosis disorder whereas Invention LIV is drawn to a method of treating or inhibiting a cell proliferative disease such as carcinoma or sarcoma. These methods are separate and distinct because they require administering an antigen-binding portion of an antibody to two distinctly different patient populations. Inventions LV-LXXXIV are separate and distinct since they require a library of antigen-binding fragments which is not required for Inventions LIII and LIV.

Inventions I-XXX and LIII, I-XXX and LIV, are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another

materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the antigen binding portions of an isolated antibody can be used to generate idiotypic antibodies.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

REQUIREMENT FOR FURTHER RESTRICTION

4. If one Invention from Groups I-XXX is elected, Applicants are required to select a

particular protein receptor tyrosine kinase for examination. Claim 4 recites 30 different protein receptor tyrosine kinases (corresponding to Inventions I-XXX). **THIS IS NOT AN ELECTION OF SPECIES.**

Receptor protein tyrosine kinases (claim 4)

I. EGFR/Erb1;

II. ErbB2/HER2/Neu;

III. ErbB/HER3;

IV. ErbB4/HER4;

V. IGF-1R;

VI. PDGFR-a;

VII. PDGFR-beta;

VIII. CSF-1R;

IX. kit/SCFR;

X. Flk2/FH3;

XI. FlkI/VEGFR1;

XII. FlkINEGFR2;

XIII. Flt4/VEGFR3;

XIV. FGFR1;

XV. FGFR2/K-SAM;

XVI. FGFR3;

XVII. FGFR4;

XVIII. TrkA;

XIX. TrkC;

XX. HGFR;

XXI. RON;

XXII. EphA2;

XXIII. EphB2;

XXIV. EphB4;

XXV. Axl;

XXVI. TIE/TIE1;

XXVII. Tek/TIE2;

XXVIII. Ret;

XXIX. ROS; and

XXX. Alk.

The receptor protein tyrosine kinases listed above are separate and distinct. They have different ligands and have different effects on downstream signaling pathways. For example, RON binds to macrophage stimulating protein (MSP) and has been implicated in the functional regulation of mononuclear phagocytes. On the other hand, IGF-1R binds to IGF, which leads to the subsequent activation of multiple signaling pathways such as Grb and PI-3K. **Therefore, Applicants are further required to elect the corresponding 2 amino acid sequences (VH and VL) of the antigen-binding portion of the antibody that binds the elected receptor protein tyrosine kinase for examination.**

VH and VL region

aa. SEQ ID NO:103 and SEQ ID NO:92;

ab. SEQ ID NO:105 and SEQ ID NO:94;

ac. SEQ ID NO:113 and SEQ ID NO:102.

ad. SEQ ID NO:104 and SEQ ID NO:93;

ae. SEQ ID NO:106 and SEQ ID NO:95;

af. SEQ ID NO:107 and SEQ ID NO:96;

ag. SEQ ID NO:108 and SEQ ID NO:97;

ah. SEQ ID NO:109 and SEQ ID NO:98;

ai. SEQ ID NO:110 and SEQ ID NO:99;

aj. SEQ ID NO:111 and SEQ ID NO:100; and

ak. SEQ ID NO:112 and SEQ ID NO:101.

The species listed above are composed of separate and distinct sequences as evidenced by the different SEQ ID NOs. The claims are drawn to multiple amino acid sequences, which are considered to be unrelated, since each sequence claimed is structurally and functionally independent and distinct due to their unique amino acid sequence and there is no alignment between the sequences to show significant similarity. A search of more than species of sequences present in these claims presents an undue burden on the Patent and Trademark Office due to the complex nature of the search in terms of computer time needed to perform the search and the

subsequent analysis of the search results by the examiner. Accordingly, applicants are required to elect one pair of sequences. Applicants are also required to point out which of the VH-CDR3 and VL-CDR3 sequences below correspond to the elected VH and VL.

VH-CDR3 and VL-CDR3

ba. SEQ ID NO: 8 and SEQ ID NO: 9;

bb. SEQ ID NO: 12 and SEQ ID NO:13;

bc. SEQ ID NO: 24 and SEQ ID NO:25;

bd. SEQ ID NO:10 and SEQ ID NO:11;

be. SEQ ID NO:14 and SEQ ID NO:15;

bf. SEQ ID NO:16 and SEQ IDNO:17;

bg. SEQ IDNO:18 and SEQ ID NO:19;

bh. SEQ IDNO:20 and SEQ ID NO:21;

bi. SEQ ID NO:22 and SEQ ID NO:23;

bj. SEQ ID NO:26 and SEQ ID NO:27; and

bk. SEQ ID NO:28 and SEQ ID NO:29.

5. If one Invention from Groups XXXI-LII is elected, Applicants are required to select one specific pair of VH and VL nucleotide sequences. Claims 11-14, 23, 25, 27, and 29 recite 22 pairs of VH and VL nucleotide sequences (corresponding to Inventions XXXI-LII). **THIS IS NOT AN ELECTION OF SPECIES.**

VH and VL nucleotide sequences

XXXI. SEQ ID NO: 84 and SEQ ID NO: 74;

XXXII. SEQ ID NO: 89 and SEQ ID NO: 75;

XXXIII. SEQ ID NO: 91 and SEQ ID NO: 76;

XXXIV. SEQ ID NO: 30 and SEQ ID NO: 31;

XXXV. SEQ ID NO: 34 and SEQ ID NO: 35;

XXXVI. SEQ ID NO: 50 and SEQ ID NO: 51;

XXXVII. SEQ ID NO: 85 and SEQ ID NO: 70;

XXXVIII. SEQ ID NO: 78 and SEQ ID NO: 67;

XXXIX. SEQ ID NO: 79 and SEQ ID NO: 64;

XL. SEQ ID NO: 86 and SEQ ID NO: 71;

XLI. SEQ ID NO: 80 and SEQ ID NO: 62;

XLII. SEQ ID NO: 87 and SEQ ID NO: 65;

XLIII. SEQ ID NO: 82 and SEQ ID NO: 73;

XLIV. SEQ ID NO: 83 and SEQ ID NO: 69;

XLV. SEQ ID NO: 32 and SEQ ID NO: 33;

XLVI. SEQ ID NO: 36 and SEQ ID NO: 37;

XLVII. SEQ ID NO: 38 and SEQ ID NO: 39;

XLVIII. SEQ ID NO: 40 and SEQ ID NO: 41;

XLIX. SEQ ID NO: 42 and SEQ ID NO: 43;

L. SEQ ID NO: 44 and SEQ ID NO: 45;

LI. SEQ ID NO: 46 and SEQ ID NO: 47; and

LII. SEQ ID NO: 48 and SEQ ID NO: 49.

The Inventions listed above are composed of separate and distinct sequences as evidenced by the different SEQ ID NOs. The claims are drawn to multiple nucleotide sequences, which are considered to be unrelated, since each sequence pair claimed is structurally and functionally independent and distinct due to their unique nucleotide sequence and there is no alignment between the sequences to show significant similarity. A search of more than one pair of sequences present in these claims presents an undue burden on the Patent and Trademark Office due to the complex nature of the search in terms of computer time needed to perform the search and the subsequent analysis of the search results by the examiner. Accordingly, applicants are required to elect one pair of nucleotide sequences.

6. If one Invention from Groups LV-LXXXIV is elected, Applicants are required to select a particular protein receptor tyrosine kinase for examination. Claim 45 recites 30 different protein receptor tyrosine kinases (corresponding to Inventions LV-LXXXIV). **THIS IS NOT AN ELECTION OF SPECIES.**

Receptor protein tyrosine kinases (claim 45)

LV. EGFR/Erb1;

LVI. ErbB2/HER2/Neu;

LVII. ErbB/HER3;

LVIII. ErbB4/HER4;

LVIX. IGF-1R;

LX. PDGFR-a;

LXI. PDGFR-beta;

LXII. CSF-1R;

LXIII. kit/SCFR;

LXIV. Flk2/FH3;

LXV. FlkI/VEGFR1;

LXVI. FlkINEGFR2;

LXVII. Flt4/VEGFR3;

LXVIII. FGFR1;

LXIX. FGFR2/K-SAM;

LXX. FGFR3;

LXXI. FGFR4;

LXXII. TrkA;

LXXIII. TrkC;

LXXIV. HGFR;

LXXV. RON;

LXXVI. EphA2;

LXXVII. EphB2;

LXXVIII. EphB4;

LXXIX. Axl;

LXXX. TIE/TIE1;

LXXXI. Tek/TIE2;

LXXXII. Ret;

LXXXIII. ROS; and

LXXXIV. Alk.

The receptor protein tyrosine kinases listed above are separate and distinct. They have different ligands and have different effects on downstream signaling pathways. For example, RON binds to macrophage stimulating protein (MSP) and has been implicated in the functional regulation of mononuclear phagocytes. On the other hand, IGF-1R binds to IGF, which leads to the subsequent activation of multiple signaling pathways such as Grb and PI-3K. Therefore, Applicants are required to elect one receptor protein tyrosine kinase for examination.

7. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

8. This application contains claims directed to the following patentably distinct species of the claimed invention.

If Applicants elect Invention III, Applicants in claim 32 are required to further elect one species from each of the following: one type of skeletal dysplasia or one type of craniosynostosis disorder

Skeletal dysplasia

da. Achondropolasia

db. Thanatophoric dysplasia (TD)

dc. hypochondroplasia

dd. severe achondroplasia with developmental delay

de. Acanthosis nigricans (SADDAN) dysplasia

OR

Craniosynostosis disorder

ea. Muenke coronal craniosynostosis

eb. Crouzon syndrome with acanthosis nigricans

The species listed above are separate and distinct. Achondroplasia is a type of genetic disorder that is a common cause of dwarfism whereas Acanthosis nigricans is a brown to black, poorly defined, velvety hyperpigmentation of the skin, usually present in the posterior and lateral folds of the neck, the axilla, groin, umbilicus, and other areas.

Crouzon syndrome affects cranial development and is characterized by craniosynostosis, as well as exophthalmos, and midface hypoplasia. Muenke

syndrome, which is a condition that results when one or more of the suture between the bones of the skull close before birth. Because of the premature closure, the skull is not able to grow in its natural shape; instead, it compensates with growth in areas of the skull where the sutures have not yet closed. This can result in an abnormally shaped head, wide-set eyes, and flattened cheekbones. Patients may also have an enlarged head, abnormalities of the hands or feet, and hearing loss. Therefore, the species are separate and distinct.

9. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 32, 36, and 37, are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

10. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

11. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

David Humphrey, Ph.D.

September 23, 2006